REMARKS

Claims 1-39 were pending prior to this Response, with claims 3, 13-16, 18 and 23-29 being withdrawn pursuant to a restriction requirement. By the present communication, page 1 of the Specification is amended to add a priority claim for the application. In addition, claims 2-4, 6, 13-16, 18 and 23-29 are cancelled without prejudice and claims 1 and 39 are amended as shown in attached Exhibit A to define Applicant's invention with greater particularity. The amendments add no new matter, being fully supported by the Specification and original claims. Accordingly, claims 1, 5, 7-12, 17, 19-22 and 30-39 are currently pending.

The Objection to the Claims

Claims 4 and 6 are objected to as allegedly failing to further limit the subject matter of a previous claim. By the present communication, claims 4 and 6 have been cancelled, rendering moot the objection to claims 4 and 6.

The Rejection under 35 U.S.C. § 102

Claims 1-2, 4-11, 19-20 and new claims 30, 31, 34, 36, 37 and 39 are rejected under 35 U.S.C. § 102 (e) as allegedly being anticipated by U.S. Patent No. 5,944,710 to Dev et al. (hereinafter "Dev"). Claims 2, 4 and 6 are cancelled, making rejection of these claims over Dev moot. With respect to the pending claims, Applicants respectfully submit that the invention methods for introducing an agent into cells in a region of tissue of a subject, as recited by amended claims 1 and 39, distinguish over the disclosure of Dev at least by reciting: "selecting a combination of a low electric field impulse of about 300 volts per centimeter to about 600 volts per centimeter and a long pulse length of about 10 milliseconds to about 100 milliseconds; and applying the low electrical field impulse in combination with the long pulse length". By the present communication Applicants have amended claims 1 and 39 to expressly

claim what was already inherent in claims 1 and 39, namely that it is the *combination* of the specifically recited low electric field impulse and long pulse length that is the crux of the present invention.

As Applicants have argued in the Response filed herein on April 8, 2002, Dev fails to disclose selection and use of the claimed combination of low electrical field impulse and long pulse length for introducing an agent into cells in a region of tissue. The Examiner appears to have not given sufficient weight to Applicants' argument that it is the *selection* of low field strength within the recited range *in combination with* long pulse length in the recited range that is a primary distinguishing factor between the present claims and the disclose of Dev.

The inventive nature of this selection and combination of parameters is described throughout Applicants' Specification (see, e.g., page 1, lines 4-5; page 2, lines 11-24; page 3, lines 29-31). In particular, Applicants teach that it is the selection and combination of these elements that distinguishes the present invention from conventional electroporation protocols:

> Many conventional electroporation protocols have used relatively high electric fields (>2,000 V/cm) delivered in a very short pulse (<1ms). This can be delivered in the form of an exponentially decaying pulse or as a uniform square wave. It is well recognized in the art that when using such parameters there is a relationship between increased voltage and the efficiency of gene delivery. However, at these voltages, benefits of increased efficiency are offset by increased cell death, which is limiting for applications where larger numbers of viable cells are desired.

(Specification, page 20, lines 10). Independent claims 1 and 39 expressly recite that the invention method comprises "applying the low electric field impulse in combination with the long pulse length" Moreover, Applicants teach (as recited above) that use of the recited combination of pulsing parameters provides a specific hitherto unknown benefit, i.e., reduced cell death. Although Dev discloses a conventional broad range of pulse conditions and pulse length, Dev does not teach, suggest, or otherwise direct those of skill in the art to select

Applicants' specific combination of parameters or that selection of the recited combination of parameters would provide the disclosed advantage of minimizing cell death.

With respect to claim 11, which recites the method of claim 1 wherein the nucleic acid is supercoiled, Applicants respectfully submit that Dev is absolutely silent regarding delivery of supercoiled nucleic acid, making a 102(e) rejection improper with respect to claim 11.

In addition, Applicants submit herewith the Declaration of Dietmar P. Rabussay under the provisions of 37 C.F.R. §1.132 in which Dr. Rabussay sets forth the factual basis for his opinion that Dev fails to teach the invention methods for introducing nucleic acid into a cell of a mammalian subject in vivo. As set forth in the Declaration, Dr. Rabussay believes that the disclosure of Dev with regard to electroporation parameters suitable for introducing nucleic acid *into mammalian cells* is substantially different than are recited in the present claims.

Therefore, based on the above arguments and the Declaration of Dietmar P. Rabussay presented herewith, Applicants respectfully submit that Dev fails to disclose each and every limitation of the invention methods, as defined by amended claims 1 (and claims dependent thereon) and 39, as would be required to establish anticipation under 35 U.S.C. § 102(e), and reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection Under 35 U.S.C. § 102(a)

Applicants respectfully traverse the rejection of claims 1-2, 4-12, and 19-20 under 35 U.S.C. § 102(a) as allegedly being anticipated by Yamazaki et al. (Biol. Repro. Dec. 1998; hereinafter "Yamazaki").

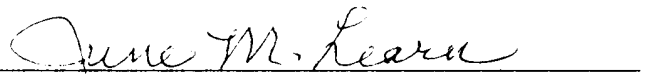
Without commenting on the merits of the Examiner's allegations, Applicants assert that Yamazaki was published after the priority date of the present application and, thus, is not

available as a reference under 102(a). By the present communication, Applicants have requested correction of the priority information for this application on page 1 of the Specification to reflect that the present application was filed June 28, 1999, as a CIP claiming priority from USSN 09/103,477, filed June 24, 1998, now abandoned. Accordingly, Applicants respectfully submit that the rejection over Yamazaki is moot and reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above amendments and remarks, reconsideration and favorable action on claims 1, 5-12, 17, 19-22 and 30-39 are respectfully requested. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: December 19, 2002



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Enclosure: Exhibit A
132 Declaration

Applicants: Nolan and Filshie
Application No.: 09/342,024
Filed: June 28, 1999
Exhibit A: Page 1

EXHIBIT A

Version with Markings to Show Changes Made

In the Specification

Please add the following paragraph as paragraph 1 of page 1 of the Specification:

--This application is a continuation-in-part application of U.S. Application Serial No. 09/103,477, filed June 24, 1998, now abandoned, each of which is incorporated herein by reference in its entirety.--

Applicants: Nolan and Filshie
Application No.: 09/342,024
Filed: June 28, 1999
Exhibit A: Page 2

In the Claims

Please cancel claims 2-4, 6, 13-16, 18 and 23-29 without prejudice.

Please amend claims 1 and 39 as follows:

1. (Twice Amended) A method for introducing nucleic acid into a cell of a mammalian subject in vivo, comprising:

contacting the mammalian subject with an isolated nucleic acid sequence via injection of the nucleic acid into the subject at a site near the cell into which the nucleic acid is to be introduced; [and]

selecting a combination of a low electric field impulse of about 300 volts per centimeter to about 600 volts per centimeter and a long pulse length of about 10 milliseconds to about 100 milliseconds; and

applying [a] the low electrical field impulse [of about 300 volts per centimeter to about 600 volts per centimeter for] in combination with [a] the long pulse length [of about 10 milliseconds to about 100 milliseconds] at or near the site of injection, wherein the impulse is of sufficient duration and strength to allow introduction of the nucleic acid into the cell.

39. (Amended) A method for introducing nucleic acid into a cell of a mammalian subject in vivo, comprising:

contacting the mammalian subject in vivo with an isolated nucleic acid sequence via perfusion of the nucleic acid into the subject; [and]

selecting a combination of a low electric field impulse of about 300 volts per centimeter to about 600 volts per centimeter and a long pulse length of about 10 milliseconds to about 100 milliseconds; and

applying [a] the low electrical field impulse [of about 300 volts per centimeter to about 600 volts per centimeter for] in combination with [a] the long pulse length [of about 10 milliseconds to about 100 milliseconds] at or near the cells into which the nucleic acid is to be introduced, wherein the impulse is of sufficient duration and strength to allow introduction of the nucleic acid into the cell.